REMARKS

The examiner relies on Licha alone as well as on Licha combined with Ohno to reject all the claims. Both rejections are unsound under US law.

Licha describes several extremely broad classes of compounds useful in its tissue visualization methods. One of the several formulas defining the genuses of compounds is that of Formula IIa, which itself encompasses a very large number of compounds. The examiner alleges that this extremely broad class generically encompasses the compounds recited in the claimed methods and thus renders such methods obvious.

However, the examiner ignores the fact that there is nothing in Licha which would lead a skilled worker toward the particular class of molecules recited in the current claims. This is why the examiner relies only on Licha's defined very broad formulas. Nothing in the reference (while very generically encompassing the claimed compounds) destroys the novelty or nonobviousness of these compounds. For instance, nothing even remotely suggests selecting compounds wherein the connecting L-containing chain is substituted only at L^4 in the way required in the claims, and sulfonic acids groups are possibly contained only at the R^{19}, R^{20}, R^{22}, R^{26} positions (but not any of the very many other possibilities recited for these positions (other than alkyl for R^{19} and R^{20} and H for R^{22} and R^{26}), and the other positions on the benzo ring are unsubstituted, and among the many Licha possibilities, X′ and Y′ are unsubstituted lower alkyl, etc. With so much picking and choosing from Licha required to arrive at the claimed compounds, the latter are clearly structurally nonobvious. See, e.g., *In re Baird*, 16 F.2d 380, 29 USPQ2d 1550 (Fed.Cir. 1994). Contrary to the examiner's allegation, the mere fact that a claimed subgenus is very generically encompassed by a prior art broad genus is not sufficient to establish prima facie obviousness. See *In re Jones*, 958 F.2d 347, 21USPQ2d 1941 (Fed.Cir. 1992), which holds this point precisely. Thus, under clear US law, the rejection must be withdrawn.

The rejection which further combines the teachings of Ohno is similarly deficient.

In this regard, it must be emphasized that all of the current claims are method claims for near infrared fluorescence imaging of a living body. Consequently, unambiguously, Ohno is not analogous prior art and cannot be relied on in an obviousness rejection. *In re Clay*, 966 F.2d 656, 23 USPQ2d 1058 (Fed.Cir. 1992). The latter decision makes clear that a reference can only

be relied on if it is in the field of the invention or it relates to a problem that the inventors were concerned with. Ohno's field is in general the field of silver halide photography. He uses dyes in a certain layer in a photographic film. This latter, e.g., is a hydrophilic colloid layer which is placed over the actual photographic active layer (photosensitive material) for the purpose of absorbing infrared light and keeping the latter from the photographic emulsion layer. See, for instance, Ohno's abstract and column 13, line 16, "prevention of irradiation," line 19, "prevention of halation," lines 24-25, "used to allow the photosensitive material to be safe from a safelight," lines 29-30 "useful as a filter dye," etc. Alternatively, the dye can be added to the photographic emulsion layer per se for the same purposes.

Thus, Ohno's field is the field of photography using silver halide photosensitive material. This is a completely nonanalogous field to that of this invention (near infrared imaging of a living body). Nor is Ohno related to the problem at hand which is the provision of infrared fluorescent contrast agents which can be used in a living body. Ohno's disclosure has no concern with whether any of its materials are safe for administration to humans. Moreover, the dyes are used to absorb radiation in order to protect the materials from that radiation. This is a completely different purpose from that of this invention where the dyes fluoresce to provide images of the inside of a human body. Ohno has absolutely nothing to do with the purpose of this invention.

Unambiguously, Ohno must be withdrawn as a reference for this reason alone. It is not analogous art and cannot be used to substantiate the rejection under 35 USC 103. Thus the rejection based on Licha and Ohno in combination is fully deficient for the reasons stated above with respect to Licha et al.

Even if one improperly relied on Ohno, the latter would not establish the obviousness of the claimed compounds because it adds absolutely nothing to Licha et al. in terms of motivation to arrive at the compounds recited in the claims of this application. For motivation, the examiner relies on the fact that Ohno teaches "that the compounds are photosensitive and they are dyes." However, Licha already teaches exactly these facts. See the title of Licha referring to its compounds as "dyes." See also the abstract, column 1, lines 7-15, etc. As for the dyes being photosensitive, of course, this is clear from the normal definition of a "dye." In any event, Licha explicitly discloses the photosensitivity of its dyes. See for example, column 8, lines 31-40. Thus, this Ohno disclosure is redundant to Licha and cannot possibly have any relevance in

motivating a skilled worker to select from Licha any particular compounds, especially since Ohno has absolutely nothing to do with either the field of the invention or the problem being solved by the invention.

Even if one ignored even this fact and still relied on Ohno, it still would not, like Licha, lead to the class of compounds recited in the claims, especially with respect to the fact that all these are sodium salts.

If one further ignored the proper application of the law to the facts at hand, the data of record would further establish the patentability of the claims, as the previous examiner recognized.

The examiner recognizes that applicants have established of record, that, unexpectedly, the sodium compounds of the invention have property differences over the closest alleged prior art compounds of Ohno, i.e., the corresponding potassium salts. However, the examiner alleges that this unexpected property difference "is not seen to be significant or practical in the context of the instantly claimed method." It is respectfully submitted that this is not a true statement and ignores fundamental considerations of pharmaceutical design.

While apparently agreeing that the data of record show low toxicity for these sodium salts in comparison to the closest prior art potassium salts, "the toxicity matters only if the compounds are to be administered in that dose range." The examiner notes that in Example 4 of the application, the compounds are administered at a dose of 5.0 mg/kg "which is far below the toxicity levels of both the sodium and potassium salts." Thus, the examiner concludes that this showing is not of practical significance.

The examiner's logic totally ignores the fundamental fact of pharmaceutical design that it is important for any agent to be administered to a living body that the difference between toxic doses and therapeutically effective doses be as large as possible. It is an important fact to know at what dose, no matter how high, toxic effects begin to occur because it is always important to have the differential between toxic dose and therapeutic dose to be as large as possible.

In support of these facts, see *Goodman & Gilman's "The Pharmacological Basis of Therapeutics," Ninth Edition, 1996, McGraw-Hill, pages 48-49.* In the bottom of the second column on page 48, this classic text defines the well-known pharmaceutical parameter of "therapeutic index." This is the ratio of LD_{50} to ED_{50} (a measure of effectiveness). This is stated

to be a measure of the selectivity of the drug, as well as its margin of safety. It is further noted that "since pharmacodynamic variation in the population may be marked, the concentration or dose of drug required to produce a therapeutic effect in most of the population will usually overlap the concentration required to produce toxicity in some of the population, even though the drug's therapeutic index may be large." Clearly, the larger the therapeutic index, the better.

That therapeutic index is an important parameter for pharmaceuticals, is further clear from the attached excerpts showing a variety of conferences ongoing (currently and for several years), involving approaches to improve therapeutic index. See the excerpts from the websites of the University of Florida College of Pharmacy Center for Drug Discovery, chemistry.org (the website of the American Chemical Society), describing an ACS short course including this topic, and an excerpt from the Napier University website, again discussing this topic and stating that "The long-term goal of the multidisciplinary research is improvement in therapeutic index..." Note also the excerpt from the Boston University Medical Campus stating in its definition of "Clinical Therapeutic Index," that "the assumption is retained that an improved or "better" drug has a *higher* Clinical Therapeutic Index."

As can be seen, the examiner's view of the data is overly simplistic. It is not only relevant that the effective dose mentioned in the Examples is lower than the LD_{50} values of the various compounds. Rather, it is also relevant and important that the difference between effective dose and LD_{50} be made as large as possible for clinical safety purposes. Because of this fact, the data of record are "significant and practical" in the context of the claimed method. As the table below shows, the therapeutic indexes (based on the 5 mg/kg dose mentioned by the examiner) in all comparison pairs are unexpectedly significantly superior for the sodium salts of this invention versus their closest prior art potassium salts.

Comp No.	LD_{50} (Na/K) (mg/kg)		TI*	
	Na	K	Na	K
31	> 3550	350	> 710	70
43	1630	300-350	326	60-70
45	1100-1220	550	220-244	110

TI (Therapeutic Index) = LD_{50} (mg/kg)/5 mg/kg

Consequently, as the PTO has previously already correctly found, even if the references of record have established a prima facie case of obviousness (which they have not for the reasons given above), the data of record would effectively rebut it for the full scope of the claims. With respect to the latter point, note that the data encompassed compounds having four or five sulfo groups, compounds having methine substituted by alkyl, sulfoalkyl, and sulfoalkyl thio (as well as a cyclic feature). The data also encompassed both ethylene and butylene linkages to the sulfo group on the ring nitrogen atom.

Once the only remaining rejections are those based on double patenting, the latter will be taken care of, if necessary, by the filing of a suitable terminal disclaimer.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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AJZ/hlw

University of Florida

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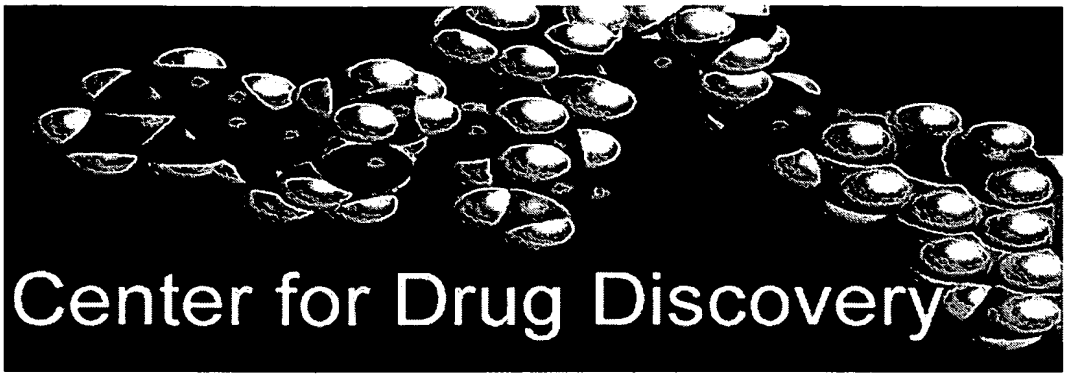

Retrometabolism Based Drug Design and Targeting Conference

This series of symposia has been extremely successful in bringing together a select group of international pharmaceutical scientists to discuss new drug design strategies in the development of safer and more effective drugs.

Introduced in 1997 the conference brings together the world's leading pharmaceutical scientists in order to discuss innovative approaches to drug design strategies. This invitation-only conference addresses research on drugs that are sequentially activated by enzymes for targeted organ/site drug delivery or improved bioavailability (chemical-enzymatic targeting systems), and also soft drugs designed to undergo predicted and directed, facile enzymatic inactivation to decrease adverse systemic effects of the drug and its metabolites. These strategies allow design of new drugs with dramatically improved therapeutic index due to their built-in metabolic activation/targeting or controlled metabolic deactivation properties. The retrometabolic based approaches have become an integral part of the general drug design and targeting approaches, and can now be widely used with the availability of the expert systems for design. Other approaches to improve the drug therapeutic index that are customarily presented at the conference include research on drug transporters, molecular complexes, and computer optimization of pharmacophores and others.

The first four (1997, 1999, 2001 and 2003) conferences were held in Florida, and successfully drew increased international participation with every event. The most recent conference was held May 8-11, 2005 in Hakone Japan due primarily to the extensive support received from Japanese participants, and was a great success. The Advisory Board members who were present at the Hakone conference met to discuss its direction, as well as plans for future symposia. Though the series' "home base" will remain in Florida, it was decided to hold the next (2007) event in Hungary. The opportunity to move the conference to a European site is particularly exciting and further expands its accessibility to the international scientific community.

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Retrometabolism Based Drug Design and Targeting

6th Retrometabolism Based Drug Design and Targeting Conference (2007, Hungary)
5th Retrometabolism Based Drug Design and Targeting Conference (2005, Hakone, Japan)
4th Retrometabolism Based Drug Design and Targeting Conference (2003, Palm Coast, FL, USA)
3rd Retrometabolism Based Drug Design and Targeting Conference (2001, Amelia Island, FL, USA)
2nd Retrometabolism Based Drug Design and Targeting Conference (1999, Amelia Island, FL, USA)
1st Drug Optimization via Retrometabolism Conference (1997, Amelia Island, FL, USA)

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- Drug Development: Lead Modification -- identification of the active part: the pharmacophore; functional group modifications; structure-activity relationships; structure modifications to increase potency and therapeutic index; quantitative structure-activity relationships; molecular graphics-based drug design.
- Receptors -- receptor structure; drug receptor interactions.
- Enzymes (Catalytic Receptors) -- enzymes as catalysts; mechanisms of enzyme catalysis; coenzyme catalysis; enzyme therapy.
- Enzyme Inhibition and Inactivation -- drug resistance; drug synergism (drug combination); reversible enzyme inhibitors; irreversible enzyme inhibitors; why inhibit an enzyme?
- DNA -- DNA structure and properties; classes of drugs that interact with DNA
- Drug Metabolism -- synthesis of radioactive compounds; analytical methods in drug metabolism; pathways for drug deactivation and elimination.
- Prodrugs and Drug Delivery Systems -- enzyme activation of drugs; mechanisms of prodrug activation.

The Instructor

Dr. J. Phillip Bowen (Course Director) is Professor of Chemistry & Biochemistry and Director of the Center for Drug Design at the University of North Carolina at Greensboro.

Course Date, Site, and Time Schedule

March 26-27, 2007, in conjunction with the 233rd ACS National Meeting
Palmer House Hilton
17 East Monroe Street
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Reserve a Guestroom through the ACS Housing Bureau

Course check-in will begin at 8:00 a.m. the first day and the course will be taught from 8:30 a.m. to 5:00 p.m.

Fee

ACS Member: $1,095
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Research

A major study is seeking to exploit matrix metalloproteinases, which degrade basement membranes of cells and contribute to the metastatic spread of cancer, as new biochemical targets for drug intervention. The long-term goal of the multidisciplinary research is improvement in therapeutic index for the patient population by targeting drugs to the site of the tumour whilst sparing normal tissue.

The research group was awarded a Proof of Concept Award by Scottish Enterprise in 2001, based on the de novo chemical synthesis of new anti-cancer and anti-arthritic drugs, prepared in latent form. The research team's novel approach seeks to exploit the few identifiable differences between tumour and normal tissue: an over-expression of certain key enzymes in tumour tissue, especially in solid tumours. The approach demands the synthesis of new anti-cancer drugs, prepared in a latent form, which are preferentially metabolised in tumour cells rather than normal cells. Active, cell-killing forms of the latent agents are released into the tumour environment by processes mediated by the key enzymes. The structure and levels of the drug-releasing enzymes vary from tumour to tumour, but the new technology allows modulation of enzyme selectivity and sensitivity by appropriate manipulation of the chemical composition of the latent form of the drug.

The new technology has a number of advantages, including: more anti-cancer drug is delivered to the tumour, there is greater selectivity for tumour versus normal cells, there is considerably reduced general toxicity for patients, fewer side-effects and is applicable to patient-centred medicine. In addition, the technology is being extended to support the development of site-specific delivery of drugs used to treat chronic inflammatory diseases or multiple sclerosis. Additionally, projects are exploiting natural, replenishable sources of chirality, including carbohydrates, for designing speciality polymers as targeted drug delivery systems (with the Faculty of Pharmacy, Paris-Sud, France).

Recently, work from the group has led to the School's first spin-out research company, supported by a Scottish Executive SMART award, to create research employment in the Biotech Sector and further support research opportunities in the School.

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C, C_x:

The concentration (in units of mass/volume) of a chemical in a body fluid such as blood, plasma, serum, urine, etc.; the specific fluid may be indicated by a subscript, i.e. C_U, the concentration of drug in the urine; when no subscript is used, C is commonly taken to be the concentration in the plasma.

C_0:

The fictive concentration of a drug or chemical in the plasma at the time (in theory) of an instantaneous intravenous injection of a drug that is instantaneously distributed to its volume of distribution. C_0 is determined by extrapolating, to zero-time, the plot of log C against t (for apparently "first-order " decline of C) or of C against t (for apparently "zero-order" decline of C).

Cf. Volume of Distribution, C_{max}, C_{ss}, First-Order Kinetics, Zero-Order Kinetics

C_{max}, C_{min}:

The maximum or "peak" concentration (C_{max}) of a drug observed after its administration; the minimum or "trough" concentration (C_{min}) of a drug observed after its administration and just prior to the administration of a subsequent dose. For drugs eliminated by first-order kinetics from a single-compartment system, C_{max}, after n equal doses given at equal intervals is given by $C_0(1 - f^n)/(1 - f) = C_{max}$, and $C_{min} = C_{max} - C_0$.

The time following drug administration at which the peak concentration of C_{max} occurs, t_p (for any route of administration but the intravenous), is given by $t_p = (\ln k_a - \ln k_{el})/(k_a - k_{el})$. (Remember that ln is the natural logarithm, to the base e, rather than the common logarithm or logarithm to the base 10; ln X=2.303 log X.)

Cf. C_{ss}, f, Multiple Dose Regimens

C_{ss}:

The concentration of a drug or chemical in a body fluid - usually plasma - at the time a "steady state" has been achieved, and rates of drug administration and drug elimination are equal. C_{ss} is a value approached as a limit and is achieved, theoretically, following the last of an infinite number of equal doses given at equal intervals. The maximum value under such conditions ($C_{ss,max}$) is given by $C_{ss,max} = C_0/(1 - f)$, for a drug eliminated by first-order kinetics from a single compartment system. The ratio $C_{ss,max}/C_0$ indicates the extent to which drug accumulates under the conditions of a particular dose regimen of, theoretically, an infinitely long duration; the corresponding ratio $1/(1 - f)$ is sometimes called the Accumulation Ratio, R. C_{ss} is also the limit achieved, theoretically, at the "end" of an infusion of infinite duration, at a constant rate.

Cf. Multiple Dose Regimens , Infusion Kinetics, First-Order Kinetics

the tubular mass is capable). Neither inulin nor PAH undergoes reabsorption by the tubules as some materials do. (N.B.: Blood and plasma are completely cleared of PAH by a single "pass" through the kidney; PAH clearance is therefore, the standard measure of renal plasma, or blood, flow).

In normal adult human males, plasma clearance of inulin is about 130 ml plasma/min; of PAH, about 700 ml plasma/min. In normal adult human females, clearance of inulin is about 115 ml plasma/min; of PAH, about 600 ml plasma/min. The relationship between clearance of blood and clearance of plasma is given by the relationship Cl_R (blood) = Cl_R (plasma)/(1-Hct), where "Hct" is the hematocrit, the proportion, as a fraction - of the blood which consists of cells, not plasma; on the average, normal adult human subjects can be assumed to have a hematocrit of about 0.45.

Like

many other physiological "constants," renal plasma clearance varies regularly and exponentially with body weight, across mammalian species (*Science 109:* 757, 1949). Renal plasma clearances, in normal animals, can be predicted using the following relationships, where Cl_R is in ml/hr, and body weight (B) is in *grams*:

$$Cl_R \text{ (inulin)} = 1.74B^{0.77}$$

$$Cl_R \text{ (PAH)} = 5.40B^{0.80}$$

Nonrenal Clearance:

Clearance by the fecal route (Cl_F), respiratory route (Cl_L), salivary route (Cl_S), biliary route (Cl_B), can be computed in a fashion analogous to computation of Cl_R: measuring the amount of substance excreted in the feces, expired air, saliva, etc., over an interval and dividing by the plasma concentration at mid-interval and the length of the interval. Following oral administration of a substance, measurement of fecal clearance may be confounded by the presence, in feces, of unabsorbed substance or of substance absorbed but excreted into the lumen of the gastrointestinal tract in, e.g., bile. Specialized techniques exist for estimating clearance of substances by the liver (Cl_H), by biotransformation and/or biliary excretion.

Unlike half-lives, clearances are directly additive and for any substance:

$$Cl_T = Cl_R + Cl_L + Cl_H + Cl_S + Cl_F + \ldots \text{ etc.}$$

Clinical Therapeutic Index:

Some indices of relative safety or relative effectiveness cannot be defined explicitly and uniquely, although it is presumed that the same quantifiable and precise criteria of efficacy and safety will be used in comparing drugs of similar kinds. The Food and Drug Administration has considered the following definition of an *improved* Clinical Therapeutic Index to be used in comparing different drug combinations or formulations; the assumption is retained that an improved or " better" drug has a *higher* Clinical Therapeutic Index " (1) increased safety (or patient acceptance) at an accepted level of efficacy within the recommended dosage range, or (2) increased efficacy at equivalent levels of safety (or patient acceptance) within the recommended dosage range."

Cf. Food and Drug Administration, Therapeutic Index, Standardized Safety Margin, Effective

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Compartment(s):

The space or spaces in the body, which a drug appears to occupy after it has been absorbed. Pharmacokinetic compartments are mathematical constructs and need not correspond to the fluid volumes of the body which are defined physiologically and anatomically, i.e., the intravascular, extracellular and intracellular volumes.

Some drugs make the body "behave" as if it consisted of only a single pharmacokinetic

GOODMAN & GILMAN'S The PHARMACOLOGICAL BASIS OF THERAPEUTICS

Ninth Edition

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be given conveniently. There is no justification for the view that more potent drugs are superior therapeutic agents. However, if the drug is to be administered by transdermal absorption, a highly potent drug is required, since the capacity of the skin to absorb drugs is limited.

Maximal Efficacy. The maximal effect that can be produced by a drug is its *maximal,* or *clinical, efficacy* (which is related to, but not precisely the same as, the term *efficacy* as discussed in Chapter 2). Maximal efficacy is determined principally by the properties of the drug and its receptor–effector system and is reflected in the plateau of the concentration–effect curve. In clinical use, however, a drug's dosage may be limited by undesired effects, and the true maximal efficacy of the drug may not be achievable. The maximal efficacy of a drug is clearly a major characteristic—of much more clinical importance than is potency; furthermore, the two properties are not related and should not be confused. For instance, although some thiazide diuretics have similar or greater potency than the loop diuretic furosemide, the maximal efficacy of furosemide is considerably greater.

Slope. The slope of the concentration–effect curve reflects the mechanism of action of a drug, including the shape of the curve that describes drug binding to its receptor (*see* Chapter 2). The steepness of the curve dictates the range of doses that are useful for achieving a clinical effect. Aside from this fact, the slope of the concentration–effect curve has more theoretical than practical usefulness.

Biological Variability. Different individuals vary in the magnitude of their response to the same concentration of a single drug or to similar drugs when the appropriate correction has been made for differences in potency, maximal efficacy, and slope. In fact, a single individual may not always respond in the same way to the same concentration of drug. A concentration–effect curve applies only to a single individual at one time or to an average individual. The intersecting brackets in Figure 3–2 indicate that an effect of varying intensity will occur in different individuals at a specified concentration of a drug or that a range of concentrations is required to produce an effect of specified intensity in all of the patients.

Attempts have been made to define and measure individual "sensitivity" to drugs in the clinical setting, and progress has been made in understanding some of the determinants of sensitivity to drugs that act at specific receptors. For example, responsiveness to β-adrenergic receptor agonists may change because of disease (*e.g.,* thyrotoxicosis or heart failure) or because of prior administration of either β-adrenergic agonists or antagonists that can cause changes in the concentration of the β-adrenergic receptor and/or coupling of the receptor to its effector systems (Caron and Leftkowitz, 1993; Carpene *et al.,* 1993; Collins *et al.,* 1992). Receptors are not static components of the cell; they are in a dynamic state that is influenced by both endogenous and exogenous factors.

Concentration–Percent or Quantal Concentration–Effect Curve. The concentration of a drug that produces a specified effect in a single patient is termed the *individual effective concentration.* This is a *quantal* response, since the defined effect is either present or absent. Individual effective concentrations usually are lognormally distributed, which means that a normal variation curve is the result of plotting the logarithms of the concentration against the frequency of patients achieving the defined effect (Figure 3–3, *A*). A cumulative frequency distribution of individuals achieving the defined effect as a function of drug concentration is the *concentration–percent curve* or the *quantal concentration–effect curve.* This curve resembles the sigmoid shape of the graded concentration–effect curve discussed above (Figure 3–2), but the slope of the concentration–percent curve is an expression of the pharmacodynamic variability in the population rather than an expression of the concentration range from a threshold to a maximal effect in the individual patient.

The dose of a drug required to produce a specified effect in 50% of the population is the *median effective dose,* abbreviated as the ED_{50} (Figure 3–3, *B*). In preclinical studies of drugs, the *median lethal dose,* as determined in experimental animals, is abbreviated as LD_{50}. The ratio of the LD_{50} to the ED_{50} is an indication of the *therapeutic index,* which is a statement of how *selective* the drug is in producing its desired effects. In clinical studies, the dose, or preferably the concentration, of a drug required to produce toxic effects can be compared to the concentration required for the therapeutic effects in the population to evaluate the clinical therapeutic index. However, since pharmacodynamic variation in the population may be marked, the concentration or dose of drug required to produce a therapeutic effect in most of the population will usually overlap the concentration required to produce toxicity in some of the population, even though the drug's therapeutic index may be large. Also, the concentration–percent curves for efficacy and toxicity need not be parallel, adding yet another complexity to the determination of the therapeutic index in patients. Finally, *no drug produces a single effect,* and, depending on the effect being measured, the therapeutic index for a drug will vary. For example, much less codeine is required for cough sup-

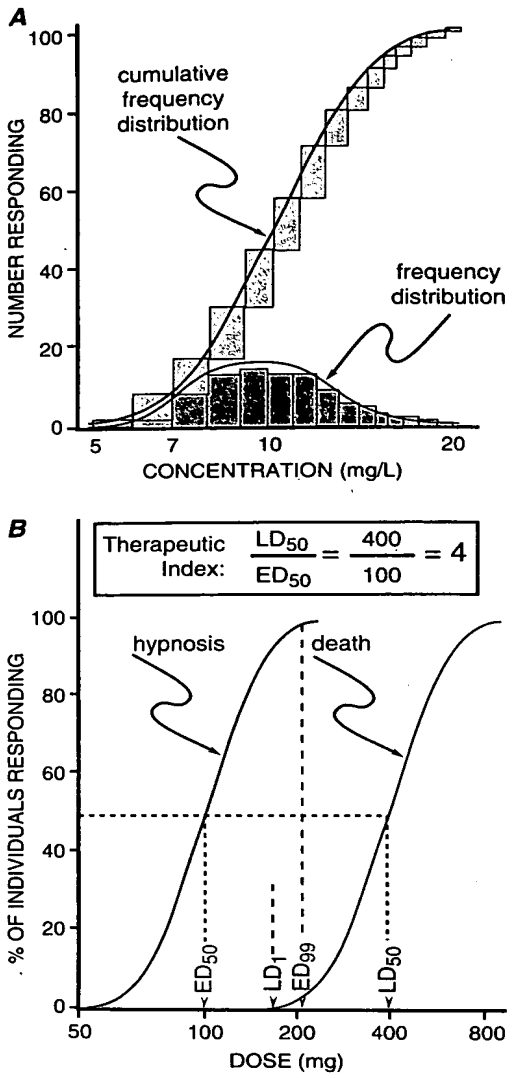

Figure 3–3. Frequency distribution curves and quantal concentration–effect and dose–effect curves.

A. Frequency Distribution Curves. An experiment was performed on 100 subjects, and the effective plasma concentration that produced a quantal response was determined for each individual. The number of subjects who required each dose is plotted, giving a lognormal frequency distribution (colored bars). The gray bars demonstrate that the normal frequency distribution, when summated, yields the cumulative frequency distribution—a sigmoidal curve that is a quantal concentration–effect curve. ***B. Quantal Dose–Effect Curves.*** Animals were injected with varying doses of sedative-hypnotic, and the responses determined and plotted. The calculation of the therapeutic index, the ratio of the LD_{50} to the ED_{50}, is an indication of how selective a drug is in producing its desired effects relative to its toxicity. (*See* text for additional explanation).

pression than for control of pain in 50% of the population, and thus the margin of safety, selectivity, or therapeutic index of codeine is much greater as an antitussive than as an analgesic.

Other Factors That Affect Therapeutic Outcome

The variation in pharmacokinetic and pharmacodynamic parameters that accounts for much of the need to individualize therapy has been discussed. Other factors, listed in Figure 3–1, also should be considered as potential determinants of success or failure of therapy. The following presentation serves as an introduction to these subjects, some of which also are discussed in Chapter 1 and Appendix II.

Age. Most drugs are developed and tested in young to middle-aged adults. At each extreme of the age spectrum individuals differ both in the way they handle drugs (pharmacokinetics) and in their response to drugs (pharmacodynamics). These differences may require substantial alterations in the dose or dose regimen to produce the desired effect in the young or in the very old.

Children. Most medications are not developed or specifically evaluated in children, and formulations often are inadequate for proper administration. Thus, development of new drugs for children, and rational use of old compounds, requires an integrated approach to pharmacokinetic, pharmacodynamic, and formulation issues. There is no reliable, broadly applicable principle or formula for converting doses of drugs used in adults to doses that are safe and effective in children. When the drug manufacturer does not provide adequate information about pediatric dosage, there can be substantial risk in deriving a dose for children and infants from an adult dose by, for example, simply reducing the dose based upon body weight or surface area. In general, pathways of drug clearance (hepatic and renal) are limited in the newborn, particularly the premature infant. The unique physiology of the newborn has led to past therapeutic disasters such as gray baby syndrome (inadequate glucuronidation of chloramphenicol with drug accumulation) and sulfonamide-induced kernicterus (displacement of bilirubin from plasma proteins in the face of increased bilirubin productions from fetal erythrocyte turnover, decreased bilirubin conjugation, acidosis, and decreased blood–brain barrier). Careful phamacokinetic studies in the newborn coupled with clinical therapeutic drug monitoring have markedly improved our knowledge of neonatal developmental pharmacology and resulted in safe therapeutics.